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(54) Sodium amide complexes

(57) Novel sodium amide complexes are disclosed being complexes of the formula

$$Na(NR_1R_2).nTMEDA$$

where R_1 is H or C_{1-20}-hydrocarbyl, R_2 is C_{1-20}- hydrocarbyl, n is an integer, (preferably 1 - 4) and TMEDA is N,N,N'N'-tetramethylethylenediamine. The complexes, which are oil soluble and substantially non-pyrophoric, are useful metallating agents in organic syntheses and have advantages over lithium diisopropylamide. The crystalline complexes are prepared by reacting a sodium alkyl, or elemental sodium, with an amine of formula R_1R_2NH in the presence of TMEDA.

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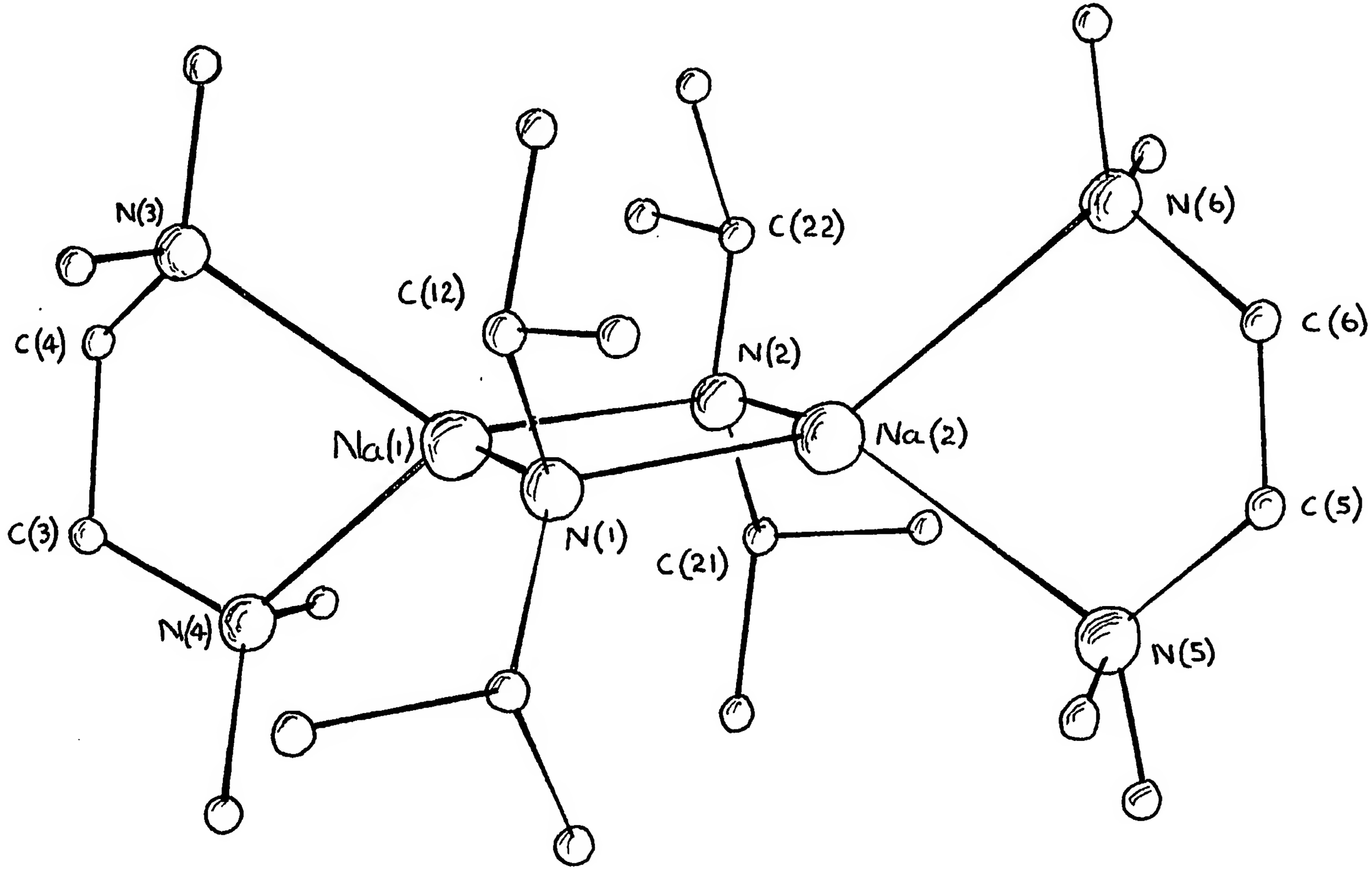
At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1990.


N(3)
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SODIUM AMIDE COMPLEXES

This invention relates to the manufacture of sodium amides, in particular complexes of sodium amide and a Lewis base.

Sodium amides, such as, sodium diisopropylamide, are the sodium analogues of lithium amides (e.g. lithium diisopropylamide used in many organic syntheses), and are potentially of great value as less expensive alternatives to the corresponding lithium compounds. However, the commercial and industrial exploitation of the sodium compounds has been handicapped by the absence of a suitable process for the manufacture of the sodium compounds on a commercial scale and by the general insolubility of sodium compounds in solvents with which they will not react.

Lithium amides, for example, may be prepared by the reaction of lithium metal with the amine, e.g. diisopropylamine, in the presence of a single electron transfer agent such as isoprene or styrene. However, attempts to repeat that process using sodium in place of lithium have resulted in poor yields of the desired amide and substantial dimerisation of the isoprene to produce, e.g. myrcene.

In our previous International Application PCT/GB93/00069 (Publication No. WO 93/14061) we have disclosed a process for the manufacture of sodium amides, in particular, sodium diisopropylamide, which comprises reacting a dispersion of finely divided elemental sodium (particle size 1-100 microns, preferably 1-30) dispersed in an organic solvent, e.g. n-octane or toluene, with the amine, e.g. diisopropylamine in the presence of a single electron transfer reagent such as isoprene. The reaction is carried out at room temperature in a hydrocarbon solvent (the same as or different from that used as the carrier component of the sodium-containing dispersion) under an inert atmosphere, e.g. of nitrogen. The product sodium amide is obtained in high yield (90-98%, based on Na metal).

In accordance with a first aspect of the present invention, that process is improved by performing the reaction in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) or by subsequently adding TMEDA to the reaction solution, to form a crystalline NDA.TMEDA complex, which has the advantages of being substantially non-pyrophoric as well as being soluble in hydrocarbons and therefore much easier to

use in subsequent reactions employing NDA as a reagent. Somewhat surprisingly performance of the process in the presence of other electron donors (Lewis base) such as pentamethyldiethylenetriamine (PMDETA), N,N,N',N'-tetraethylethylenediamine (TEEDA), 1,4-diazobicyclo-[2.2.2.]-octane (DABCO), 1,3-dimethylimidazolidinone (DMI) and 1,3-dimethyl-3,4,5,6-tetrahydro-2 (1H)-pyrimidinone (DMPU) does not result in the formation of a crystalline complex.

Alternatively, such complexes can be prepared by reacting a sodium alkyl (e.g. n-butyl sodium) with the amine, e.g. diisopropyl-amine in a hydrocarbon medium, e.g. n-hexane, either in the presence of TMEDA or by adding TMEDA to the reaction medium to redissolve the initial precipitate, followed by crystallisation of the crystalline complex, preferably by refrigeration.

In accordance with the present invention, therefore, there are provided, as novel compositions, crystalline sodium amide complexes of the formula

$$Na(NR_1R_2).nTMEDA$$

where R_1 is H or a hydrocarbyl (preferably alkyl) group of 1-20 carbon atoms, and preferably lower (C_1-C_8) alkyl, R_2 is a hydrocarbyl group as defined for R_1, and n is a small integer e.g. 1-4, and usually 1. Preferably R_1 and R_2 are both hydrocarbyl, preferably C_1-C_8 alkyl and most preferably isopropyl.

Sodium amide complexes of the above formula are useful alternatives to lithium amides, and especially to lithium diisoproylamide (LDA), used as metallating reagents in many organic syntheses, and where the solubility of the NDA.TMEDA complex in low polarity solvents such as n-hexane, cyclohexane and toluene is beneficial. Such complexes also have the advantage of being substantially non-pyrophoric, although still somewhat sensitive to air and moisture.

Sodium amide/TMEDA complexes of the above formula may be prepared by either of the two routes mentioned, that is to say either by reacting sodium metal dispersed in a hydrocarbon carrier liquid with an amine (R_1R_2NH, where R_1 and R_2 are as above defined), the reaction being carried out under an inert atmosphere, e.g. under nitrogen, in a

hydrocarbon solvent (the same as or different from the said carrier liquid) and in the presence of a single electron transfer agent, preferably isoprene and TMEDA, or by reacting a sodium alkyl with an amine in a hydrocarbon solvent, that reaction being carried out either in the presence of TMEDA, or by subsequently adding TMEDA to the reaction medium to redissolve the precipitate.

In either case, the complex is recovered in crystalline form by allowing the reaction solution to stand at room temperature or by refrigeration.

In the first of the above processes i.e. the reaction of finely divided sodium metal with an amine and TMEDA in the presence of an electron transfer agent and a hydrocarbon solvent, the process is carried out under anhydrous conditions using pre-dried reactants and an excess of amine relative to sodium metal to drive the reaction to completion. Reaction is performed at room temperature under an inert atmosphere, e.g. an atmosphere of nitrogen, with from 1-2 equivalents of TMEDA, or thereabouts, i.e. a small molar excess.

The reaction is carried out in an inert hydrocarbon, non-donor solvent, preferably n-hexane or cyclohexane, although other hydrocarbons may be used.

As indicated the sodium reactant used is a dispersion of sodium metal in an inert solvent, preferably a hydrocarbon solvent such as n-octane or toluene. The particle size range of the dispersed sodium is not particularly critical, but will usually be in the range 1 to 500 microns, preferably 1-100 microns and more preferably 1-30 microns.

The reaction is carried out in the presence of a single electron transfer agent, preferably isoprene by reason of its volatility and ease of removal at the end of the reaction. Other reagents capable of effecting single electron transfer between the two reagents, i.e. the sodium metal and the amine, may be used. The amount of single electron transfer agent present in the reaction medium is not critical, but preferably the amounts of amine and single electron transfer agent will be equimolar or thereabouts.

The reaction of the invention is applicable to the preparation of a wide range of sodium amides derived from a variety of primary and secondary aliphatic and aromatic amines, preferably secondary amines such as diisopropylamine and other di (lower) alkyl-amines (lower = 1

to 8 carbon atoms), diphenylamine, dicyclohexylamine, dibenzylamine, 2,2,6,6-tetramethylpiperidine, etc. Suitable primary amines include methylamine, ethylamine, t-butylamine, 2-ethylhexylamine etc. There is no theoretical limit to the molecular weight of the amine, practical and utility considerations indicate applicability in general to aliphatic and aromatic primary and secondary amines containing up to 24 carbon atoms, total, more usually 1 to 20 total.

The first process according to this invention is illustrated by the following Example.

EXAMPLE 1

74 mmol Sodium (30% w/w dispersion in n-octane, particle size, circa 30 microns) was added to a solution of diisopropylamine (105 mmol), isoprene (105 mmol) and TMEDA (75 mmol) in n-hexane (35 ml). An exothermic reaction occurred during which the sodium quickly dissolved to yield a dark red solution. The solution was filtered to remove unreacted sodium and cooled in a refrigerator. A red crystalline product was obtained (75% yield), m.p. 88-94°C. Further crystallographic data see Example 2.

The alternative reaction is carried out using approximately equimolar quantities of the amine, preferably diisopropylamine, and the alkyl sodium, preferably sodium C_1-C_5 alkyl, e.g. n-butyl sodium. The reaction is carried out at room temperature under an inert atmosphere (argon or nitrogen), in a hydrocarbon solvent, e.g. n-hexane, and optionally containing a molar excess (relative to amine) of TMEDA. Alternatively a molar excess of TMEDA is added at the end of the reaction to redissolve the initial precipitate with gentle warming, followed by cooling the reaction medium to provide a crystalline product. All reagents are predried.

Suitable amine reactants and solvents are as described above for the first reaction.

The alternative preparative route is illustrated by the following Example.

EXAMPLE 2

n-Butyl sodium (10 mmol) was suspended in 10 ml. of dried n-hexane under a protective atmosphere of argon. Diisopropylamine (10 mmol) was added, resulting in an exothermic reaction and the formation of a precipitate. This was redissolved by adding TMEDA (20 mmol) to the reaction solution, and warming gently, to provide a pale orange solution. Recooling to room temperature provided a crop of pale yellow/fawn crystals (31% yield; first crop), with a second crop being recoverable on refrigeration, m.p. 88-94°C.

Crystallographic studies show the complex to be dimeric, having a crystal structure as shown in the accompanying drawing. This structure comprises a dimeric arrangement, consisting of a planar $(NNa)_2$ cyclic ring with TMEDA-chelated Na^+ cations. Each Na^+ cation and each (amido) nitrogen anion within the ring are four coordinate. Their local geometries are pseudo-tetrahedral. The average N-Na ring bond length is 2.449Å. Internal bond angles are 103.5deg and 76.5deg at Na and N respectively. Attached isopropyl groups occupy positions above and below the $(NNa)_2$ ring plane. The TMEDA donor ligands complex the metal centres in their normal didentate manner. These dative N-Na bonds are decidedly longer (average length, 2.618Å) than the N-Na ring bonds. Both nitrogen atoms of each TMEDA molecule also display four-coordinate distorted tetrahedral geometries.

This structure is in marked contrast to the infinite helical arrangement of crystalline LDA prepared in an analogous manner.

Crystallographic data: $C_{24}H_{60}N_6Na_2$,

M_r = 478.8, monoclinic, $P2_1$, a = 8.633(1), b = 19.119(3), c = 10.390(1)Å, ß = 108.03(1)°, V = 1630.8Å^3, Z = 2, D_x = 0.975 gcm^{-3}, λ (Cu Kα) = 1.54184Å, μ = 0.66 mm^{-1}, F(000) 536, T = 240K.

The crystals are soluble in n-hexane and toluene and are non-pyrophoric but decompose slowly in the presence of air or moisture.

The reactivity and selectivity of the crystalline NDA.TMEDA of this invention have been investigated and the results are indicated below:

Reactivity:

Preparation of Diphenylacetic Acid from Diphenylmethane - Experimental Procedure

Diphenylmethane (2 mmol) was added to a solution of each metallating agent, n-butyl lithium, LDA, NDA and NDA.TMEDA (2.2 mmol), in cyclohexane (5 ml) and tetrahydrofuran (2 ml), under nitrogen, and the resulting solution was stirred at room temperature for 30 minutes.

After this time, the reaction product was poured onto cardice and the cardice was allowed to evaporate. A solution of 1M NaOH was added, followed by diethylether, and the aqueous layer was separated and acidified to pH1. The resulting product, diphenylacetic acid, was then extracted into diethylether, dried and concentrated *in vacuo*. The product was analysed by GC/MS.

The yields of diphenylacetic acid, based on diphenylmethane are given in Table 1 and show that the NDA.TMEDA complex of this invention provides yields entirely equivalent to those obtained with non-complexed NDA (prepared according to the process described in PCT/GB93/00069, i.e. by the procedure described herein in Example 1, but omitting the TMEDA from the reaction medium) and higher than those obtained using the more traditional metallating agents n-BuLi and LDA.

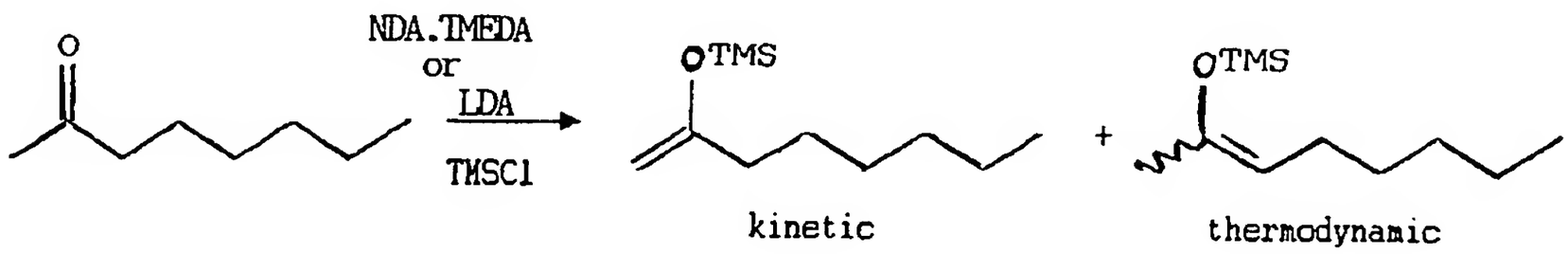
TABLE 1

Base	Yield (%)
n-BuLi	75
LDA	54
NDA	87
NDA.TMEDA	87

Selectivity:

The selectivity of NDA.TMEDA according to this invention has been compared with that of LDA by the means of the formation of silyl enol

ethers from 2-octanone and 2-methyl-cyclohexanone, viz the reactions:



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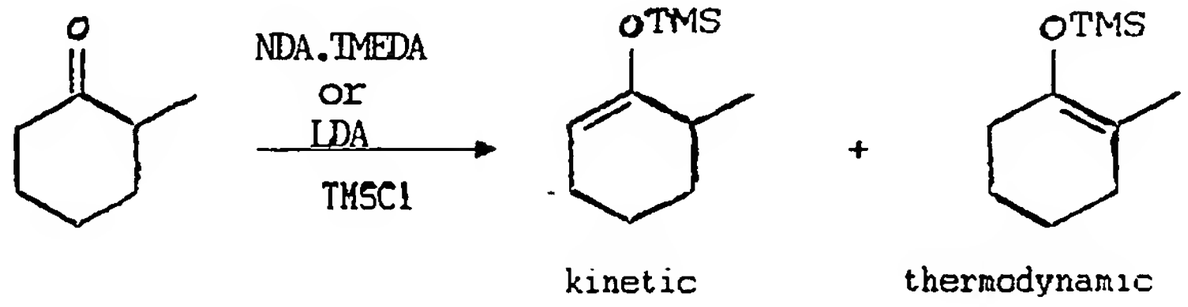

Experimental Procedures

A solution of crystalline NDA.TMEDA (1.72mmol) (prepared as in Example 1) in THF (5ml) was added dropwise to a solution of trimethylsilylchloride (11.7 mmol) and 2-octanone (1.56mmol) in THF (6ml) at -70°C. Triethylamine (22mmol) was added after a minute and the cooling bath was removed. Saturated $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was washed with petroleum ether and the combined organic extracts were washed first with water and then with 0.1M nitric acid. Drying and concentration in vacuo afforded the required kinetic (K) and thermodynamic (T) enol ethers, which were analysed by GC/MS to determine the K:T ratio.

For the corresponding reaction with LDA prepared in situ, the method used was that according to E. J. Corey and A. W. Gross, in Tet. Lett. 1984, 25, 495. The LDA was prepared by the addition of diisopropylamine (5.5 mmol) to a solution of n-BuLi (5.5 mmol) in THF (7 ml) at -50°C.

The selectivities obtained, i.e. the K:T ratios are given in Table 2.

TABLE 2

Reagent	K:T Ratio
LDA	93.5:6.5
NDA.TMEDA	94.3:5.7

2-Methylcyclohexanone (2.5 mmol) was added to a solution of NDA.TMEDA (2.7 mmol) prepared as in Example 1 in THF (10 ml) at -70°C and the resulting solution stirred at -70°C for 20 minutes. TMSCl (2.8 mmol) was added and the mixture allowed to warm up to room temperature. After a further 30 minutes the mixture was quenched with $NaHCO_3$ and extracted into n-hexane. The ratio of kinetic (K) to thermodynamic (T) enol ethers was determined by GC/MS. The results are presented in Table 3.

In the comparative experiment, the LDA was prepared *in situ* in the same manner as before.

TABLE 3

Reagent	K:T Ratio
LDA	95.6:4.4
NDA.TMEDA	94.1:5.9

As will be seen the selectivities with NDA.TMEDA are entirely comparable with those obtained with the known reagent LDA.

CLAIMS

1. Crystalline sodium amide complexes of the general formula $Na(NR_1R_2).nTMEDA$, where R_1 is H or a hydrocarbyl group of upto 20 carbon atoms, R_2 is a hydrocarbyl group as defined for R_1, n is an integer and TMEDA is tetramethylethylenediamine.

2. Complexes according to claim 1, where R_1 and R_2 are both C_1-C_8 alkyl.

3. Complexes according to claim 1 or 2, where n is 1.

4. Crystalline sodium diisopropylamide.TMEDA.

5. A method for the preparation of crystalline sodium amide complexes according to claim 1, which comprises reacting elemental sodium dispersed in a hydrocarbon carrier liquid with an amine of the formula R_1R_2NH, where R_1 and R_2 are as defined in claim 1, the reaction being carried out in the presence of a hydrocarbon solvent and in the presence of N,N,N',N'-tetramethylethylenediamine and a single electron transfer agent and under an inert atmosphere, and cooling the reaction solution to recover the crystalline product.

6. A method according to claim 5, wherein the reaction is carried out in the presence of isoprene as the said single electron transfer agent.

7. A method for the preparation of crystalline sodium amine complexes according to claim 1, which comprises reacting a sodium alkyl with an amine of the formula R_1R_2NH, where R_1 and R_2 are as defined in claim 1, the reaction being carried out in a liquid hydrocarbon medium and under an inert atmosphere, N,N,N',N'-tetramethylethylenediamine either being present in the reaction medium or added thereto at the end of the reaction in molar excess relative to the amine to dissolve the initial precipitate, and cooling the reaction medium to recover the crystalline product.

8. A method according to claim 7, wherein the sodium reactant is n-butyl sodium.

9. A method according to any one of claims 5-8, wherein the amine reactant is a di(C_1-C_8)alkylamine.

10. A method according to claim 9, wherein the amine reactant is diisopropylamine.

Patents Act 1977 **Examiner's report to the Comptroller under Section 17** **(The Search report)**	Application number GB 9316121.4
Relevant Technical Fields (i) UK Cl (Ed.L) C2C (CNC) (ii) Int Cl (Ed.5) C07C	Search Examiner S J QUICK Date of completion of Search 21 OCTOBER 1993
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASE: CAS ONLINE	Documents considered relevant following a search in respect of Claims :- 1-10

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	J Chem. Soc., Chem. Commun., 1991, vol (7), pages 497-498, P C Andrews et al, "A new type of structure in sodium amide ring chemistry:", see whole document	1 and 3

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).